Basics of Magnetic Resonance Spectroscopy for the Practicing Clinician

Jeffry R. Alger, PhD
Department of Neurology
Department of Radiological Sciences
Ahmanson-Lovelace Brain Mapping Center
David Geffen School of Medicine at UCLA
University of California, Los Angeles
Los Angeles, California, USA

I. Introduction

Magnetic resonance spectroscopy (MRS) detects electromagnetic signals produced by the atomic nuclei within molecules. It can be used to obtain *in situ* concentration measures for certain chemicals in living tissue. This presentation will introduce the physics and technology of MRS signal detection at a basic level. It will also introduce basic biochemical concepts that are useful for interpreting spectra.

II. Basic MRS physics and technology

MRS is essentially identical with nuclear magnetic resonance (NMR) spectroscopy, which has been used in chemistry or physics for the past half century. The term "MRS" has been used for biomedical NMR spectroscopy applications since the 1980s. Terminology that eliminates "nuclear" reflects that neither "radioactive nuclei" nor "radiation" are parts of clinical MRS studies.

MRS is viewed by the radiology and medical imaging communities as member of a large family of "MRI techniques". In MRS, magnetic resonance signals are detected from chemical compounds other than water with the goal generally being to evaluate *in vivo* biochemistry, whereas the magnetic resonance signals used to generate MRI "pictures" are most often produced by the water in living tissue. Otherwise MRS and MRI share the same signal detection technology and therefore MRS studies can be performed using the same equipment that is used for MRI.

MRS can be understood at a basic level through discussion of each of the component terms (i.e., magnetic, resonance, and spectroscopy). MRS is based on the fact that certain atomic nuclei behave as spinning bar magnets. These "nuclear magnets" produce a magnetic field that can interact with an externally applied magnetic field. It is through this "magnetic interaction" that energy can be exchanged between the nuclear magnetic fields and the externally applied field. Energy exchange of this sort is known as "resonance". In physics and chemistry, the term "spectroscopy" is used to describe the study of the specific oscillation frequency (or wavelength) at which an energy exchange interaction occurs. In the typical MRS study, the frequency of the magnetic interaction has an oscillation that is similar to that of the electromagnetic waves used in radio and television communication.

MRS requires that the body be placed in a strong time-invariant (i.e. static) externally applied magnetic field. Typical human MRS protocols use a magnetic field of 1.5 Tesla or higher. MRS signal strength generally improves as the static magnetic field strength is increased, so it is desirable to use the strongest magnetic field available. A second externally applied magnetic field, whose strength oscillates as radio waves do (e.g. 63 MHz) , is also necessary. It is

through this oscillating magnetic field that the specific interaction frequencies can be detected (i.e., the spectroscopy). The term "radio frequency (rf) field" is often used to denote this oscillating magnetic field. The device that produces the rf field is the rf coil, which must be placed around or very near to the body part being examined.

The basic procedure for acquiring MRS data is to place the subject in the strong static magnetic field and also within an rf coil. The rf coil is then turned on (i.e. pulsed) very briefly to create an rf field that interacts with a broad range of different types of atomic nuclei within the sample. Once the rf pulse is turned off, the magnetic interaction between the nuclear magnetism and the static magnetic field produces distinct electromagnetic signals in the rf coil. These signals are subjected to analog and digital processing resulting in an MR spectrum.

The MR spectrum is a two-dimensional plot of frequency on the horizontal axis and intensity of resonance interaction (i.e. signal) on the vertical axis (Figure 1 (insets)).

Many variants of this basic procedure are available to meet specific needs. The rf pulse is usually turned on and off more than once during the data acquisition and the term "pulse sequence" is used to convey the idea that the data are generated by a complicated series of pulses designed to meet specific experimental needs. These experimental needs include such things as defining the anatomic location from which signals are detected (i.e. spatial localization) and simplifying (i.e. editing) the spectrum so that only a few key signals can be detected with clarity and therefore measured with the greatest possible degree of accuracy.

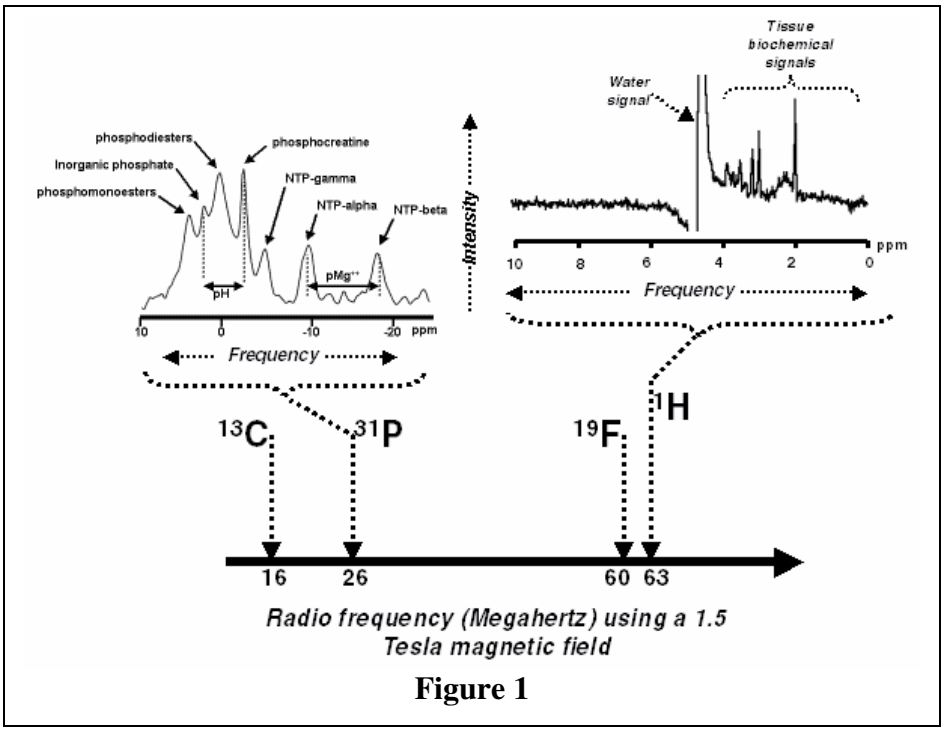

Figure 1

Special hardware known as gradient coils are also located within the MRI scanner and these can be turned on and off at the appropriate times during the pulse sequence. These coils are capable of causing the static magnetic field strength to depend on location and are used in conjunction with rf pulses to achieve spatial localization. Two complementary methodologies are available for attaining volume localization. In localized single volume MRS, a conventional MR image is first obtained and then used to identify a location of interest which is typically defined as a rectilinear "voxel". The MRS signal is then acquired from only this location using a pulse sequence that is designed to optimally detect signal produced by the defined region and to suppress to the greatest degree possible signal that arises from nuclei in other regions. The

alternative method is magnetic resonance spectroscopic imaging (MRSI). In MRSI studies, MRS signals are simultaneously acquired from a grid containing a large number of rectilinear voxels that include the tissue of interest. MRSI is also sometimes referred to as "multivoxel MRS", "spectroscopic imaging (SI)" or "chemical shift imaging (CSI)".

The random movement of electrically charged particles (e.g. sodium ions) within the living tissues produces random magnetic fields that appear as "noise" in the MR signal detection system and this noise appears as random baseline fluctuations in the MR spectrum (Figure 2). MRS signals generated by living tissues are generally similar in magnitude to this noise and accordingly there is some uncertainty associated with MRS signal measurements. The signal to noise ratio (SNR) can be enhanced by repeating the signal detection procedure multiple times and averaging the results. Signal averaging is productive because the desired signal is identical on each repeat, whereas the noise is random and therefore differs for each repeat. The disadvantage of signal averaging is that it is time consuming. The need for signal averaging is one of the reasons that MRS studies require more time than many other types of MRI studies. Alternatively the SNR can be increased by making measurements from a larger tissue volumes. This is because the noise arises from the entire body part that is within the rf coil, while the signal arises from only within the defined volume of interest. The relatively unfavorable SNR characteristics of MRS result in MRS volume resolution that is relatively poor compared to many other MRI techniques.

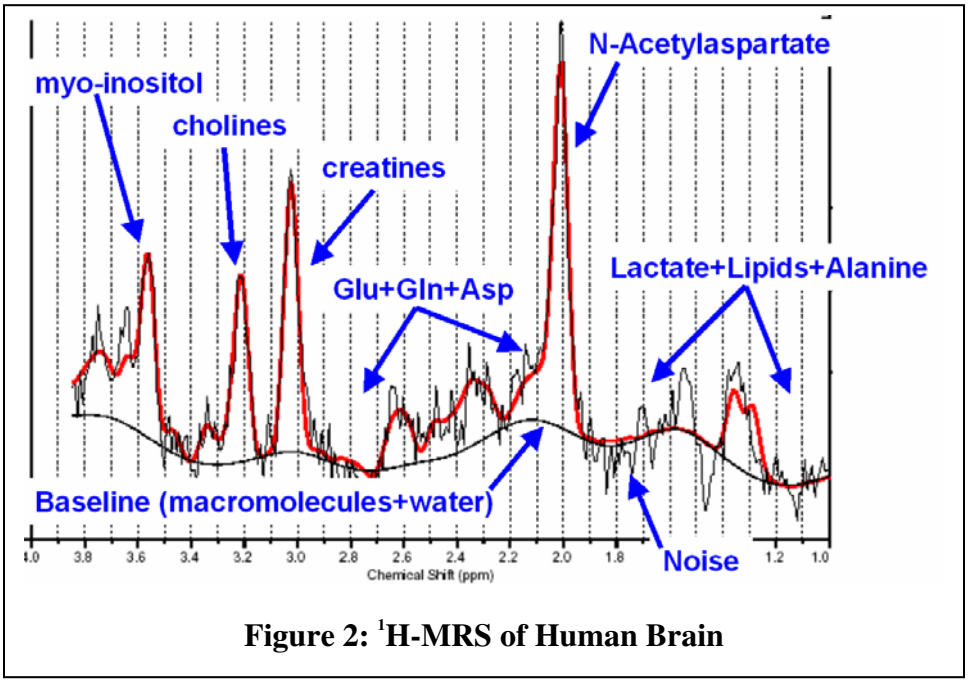

Figure 2: ^{1}H-MRS of Human Brain

Only certain atomic nuclei (isotopes) of biological significance (e.g. ^{1}H, ^{31}P, ^{13}C, ^{7}Li and ^{19}F) have suitable magnetic properties and are therefore capable of producing MRS signals. MRS signals produced by these isotopes are easily distinguished from each other by their much different characteristic frequencies (Figure 1). The ability of MRS to detect unique signals from the same type of nucleus (i.e. ^{1}H) present in different chemicals results from the fact that the magnetic resonance frequency is directly proportional to the static magnetic field strength at the nucleus. The electrons which surround the atomic nuclei circulate in ways that tends to alter the magnetic field at the nucleus to a small extent but significant extent. This causes small but detectable alterations in the MRS signal frequency which are dependent on the chemical structure surrounding an atomic nucleus, allowing the identification of specific resonance signals from individual nuclei within individual molecules (Figures 2 and 3). The differences in frequency resulting from chemical structure are referred to as "chemical shifts". Important MRS signals from a particular isotope, such as ^{1}H, may be separated from each other in frequency by only a few cycles per second (Hertz) with each of their signals having a frequency of millions of cycles per second (Megahertz (MHz)). For this reason, it is a common practice to specify the chemical shift in "parts per million (ppm)".

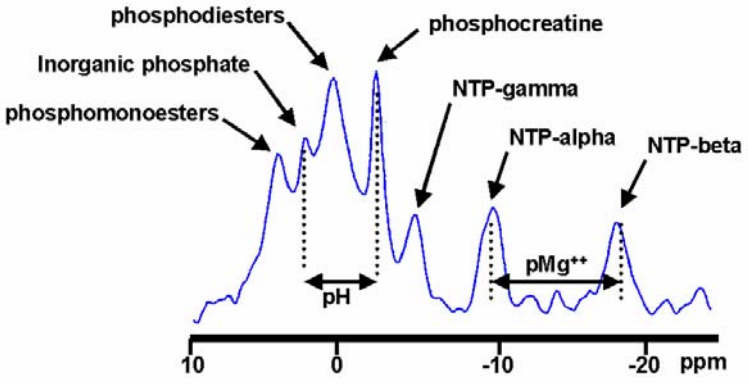

Figure 3: 31P-MRS of Human Brain

The different nuclei of biological significance have different attributes and practical limitations with respect to MRS detection. The proton (^{1}H) produces the strongest most easily detected MRS signal and is therefore most frequently used for routine clinical MRS. Moreover, ^{1}H MRS is most convenient in that it can be performed using the same hardware as is used for conventional MRI. ^{31}P produces the second most intense set of MRS signals. Figures 2 and 3 illustrate the features that are seen in ^{1}H- and ^{31}P-MRS of brain tissue. ^{31}P-MRS has been the basis for some clinical MRS examinations, but the technical difficulty associated with detection of ^{31}P signals compared to ^{1}H-MRS signals has led to far more common use of ^{1}H-MRS in recent years. Other atomic nuclei are of research interest, but are not presently used in routine clinical MRS studies.

MRS has a strict requirement for a spatially homogeneous static magnetic field. The applied static magnetic field intensity must vary by less than approximately 100 parts per billion over the intended sampling volume. Anatomic features of the anatomy surrounding the tissue of interest can distort the shape and intensity of the applied magnetic field to an unacceptable extent introducing problems with detection of MRS signals from certain body regions. Similarly the presence of certain magnetic materials such as hemoglobin degradation products or paramagnetic contrast agents can also be a problem. In addition, the study of patients who have had surgeries prior to their MRS examinations can sometimes be problematic as a result of magnetic materials that are left in the body during the surgical procedure.

Magnetic resonance instruments can provide a highly accurate measure of signal frequency, but are limited in their ability to provide exact measures of signal amplitude (the area

under the signal) that are calibrated against a defined universal standard. Hence, MRS permits ready conclusions about whether a particular molecule's signal is present above the noise level, but tissue concentration measurements are less precise. Furthermore, measures of signal intensity must be quoted with reference to some "calibration" signal that is also present in the spectrum being analyzed or that can be acquired from some other MRS or MRI measurement. For this reason, MRS results are often reported as the ratio of two signals although more recent studies have emphasized the utility of more absolute approaches to quantification of the concentration of signal producing compounds.

Special problems related to signal overlap apply to ^{1}H-MRS. The tissue water signal is very large relative to the signals produced by tissue chemicals and it overlaps with some chemical signals rendering them hard to identify and measure. Therefore the pulse sequences used in ^{1}H-MRS usually have a water signal suppression component that is designed to suppress water signal relative to tissue chemical signals. The fatty acyl components of certain lipid molecules, such as the triglycerides in adipocytes, also produce strong signals that overlap with desired MRS signals and these can be problematic as well. Interestingly other lipid molecules, such as the phopholipids in biological membranes, do not produce large interfering MRS signals. This means that ^{1}H-MRS signals can only be detected from tissues that do not contain a substantial amount of triglyceride even though biological membranes are present. Localization procedures that suppress signals from adipose tissue are often the means that are used to suppress lipids signals.

III. Basic biochemistry concepts

MRS can not detect signals generated by molecules having molecular weights greater than a few thousand daltons or by smaller molecules that are bound to macromolecular arrays (e.g. proteins, membranes or nucleic acid polymers). Only the small mobile molecules present within tissue can be detected with MRS. Typically, such tissue-associated small molecules are "metabolites" involved in intermediary metabolism. Accordingly MRS is often said to detect "tissue metabolites", and from this comes the somewhat inaccurate generalization that MRS "measures" metabolism. In this light, MRS is frequently discussed in association with certain nuclear medicine imaging procedures, such as fluorodeoxyglucose positron emission tomography, which are designed to measure metabolic rates through the use of radioactively-labeled tracer molecules. In fact, radiotracer imaging technologies and MRS do not sense metabolism is precisely the same manner. MRS detects the signals produced by certain metabolites that are inherently present in the tissue. With appropriate calibration, such measures can be used to obtain the tissue metabolite concentration. This is inherently different from measuring the rate of a metabolic pathway as is done in radiotracer imaging.

MRS has an inherently low sensitivity compared to many destructive techniques for detecting molecules in tissue. Indeed, only a few of the most heavily concentrated tissue molecules are readily detected with MRS. For ^{1}H-MRS signal detection, the standard rule of thumb is that there must be at least 1 micromole of the molecules of interest within the volume of interest.

In order for MRS to be useful in the evaluation of a particular disease, the disease must alter the concentration of some tissue metabolite that can be detected with MRS. More often than not a clear understanding of how a particular disease alters the biochemistry of MRS-dectectable metabolites is not available. Instead an empirical approach has been employed. Indeed, much of

the altered biochemistry that is exploited in clinical MRS studies was "discovered" by doing exploratory *in vivo* MRS studies.

IV. Conclusion

MRS provides a means of measuring the concentrations of the more concentrated tissue metabolites using "MRI technology". MRS measurements are made with regional specificity and without exposure to ionizing radiation. Detection and evaluation of disease using MRS has been largely based on the study of particular diseases with MRS.

V. Further Reading

Alger JR. MRS of the Brain. in Encyclopedia of Neuroscience (ed. Adelman G, Smith BA). Elsevier Science (2004)

Barker PB. Fundamentals of MR spectroscopy. In *Clinical MR Neuroimaging. Diffusion, Perfusion and Spectroscopy*. (eds. Gillard JH, Waldman AD, Barker PB). Cambridge University Press 2004.

Danielsen ER, Ross BD. Magnetic Resonance Spectroscopy Diagnosis of Neurological Disease. Marcel Dekker. 1999. Chapters 1-3.